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ORIGINAL ARTICLE

Diagnostic Value of Conventional and Doppler Ultrasound Findings in Liver Fibrosis in Patients with Chronic Viral Hepatitis

Yasmin Davoudi [1], Parvaneh Layegh [1], Hamidreza Sima [2], Shiva Tatari [3], Roya Faghani [3*]

[1] *Department of Radiology, School of Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences,* [2] *Department of Gastrointestinology, Mashhad University of Medical Sciences, and* [3] *Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran*

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Background: The main outcome of virus-related hepatitis is progression to liver fibrosis. Therefore, early diagnosis is very important in the treatment and management of patients. Although liver biopsy is the gold standard test for assessment of liver fibrosis, it is expensive and has some disadvantages such as sampling errors, interobserver variability, and a significant mortality and morbidity rate. Moreover, this method is invasive and has side effects, especially if it needs repeated sampling. In order to come up with a reliable noninvasive modality in place of biopsy, we studied the value of grayscale ultrasonography (US) and Doppler ultrasonography (DS) for the diagnosis of liver fibrosis in patients with chronic viral hepatitis.
Patients and methods: Sixty patients, 43 with chronic hepatitis B and 17 with chronic hepatitis C, were enrolled in this study. Grayscale US and DS were performed for all patients in the week prior to liver biopsy. Ultrasonographic findings were recorded according to a US scoring system, and they were compared with histological findings after liver biopsy.
Results: A total of 35 male (mean age: 36.1 ± 10.1 years) and 25 female (mean age: 36.1 ± 10.4 years) patients were studied. Forty-three patients had chronic hepatitis B and the others had chronic hepatitis C. The overall grayscale US score was abnormal (ranged from 1 to 7) in 63.3% of patients and normal (0) in the other patients. The mean portal vein velocity ranged from 8.1 cm/s to 31.7 cm/s (mean: 17.1 ± 5.1 cm/s). The right hepatic vein diameter ranged from 2.8 mm to 8 mm (mean: 5.1 ± 1.2 mm). The total DS score was abnormal (1 or 2) in 66.7% of patients. Quantitative US parameters that were related more significantly to the histopathological staging scores of liver fibrosis were mean portal vein velocity, right hepatic vein diameter, and gallbladder wall thickness. The total grayscale US score, DS score, and

Conflicts of interest: The authors declare that there are no conflicts of interest.

* Correspondence to: Dr. Roya Faghani, Radiology Department, School of Medicine, Imam Reza Hospital, Ibn Sina Street, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail address: Faghaniroya@yahoo.com (R. Faghani).

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accumulation of US and DS scores (US—DS score) were significantly different between patients with liver fibrosis and those without fibrosis ($p = 0.03$, $p = 0.03$, and $p < 0.001$, respectively). We found that the total grayscale US score, DS score, and US—DS score are significantly correlated with liver fibrosis stages.

Conclusion: Based on these findings, one can conclude that US may be an accurate, noninvasive alternative modality for the diagnosis of liver fibrosis, with fewer side effects than biopsy. It may be especially useful for repetitive follow-up of patients.

Introduction

Chronic viral hepatitis is a common cause of hepatic fibrosis and cirrhosis [1—3]. Accurate determination of the amount of fibrosis has significant therapeutic and prognostic roles in the management of patients with chronic viral hepatitis [4]. Although liver biopsy is the gold standard test for the assessment of liver fibrosis [5], it is invasive and has a significant mortality and morbidity rate. The complication rate of hepatic biopsy ranges from 1% to 5%, and its mortality ranges from 1 in 1000 to 1 in 10,000 [6—8]. In addition, liver biopsy is associated with significant sampling error and interobserver variability [9,10]. It is estimated that liver biopsy leads to false-negative results in 20—30% of patients [11—13]. Therefore, finding a reliable, noninvasive procedure that can be used repeatedly in follow-up for differentiation between liver fibrosis and cirrhosis seems to be important. Ultrasonography (US) is considered a noninvasive and inexpensive method for the diagnosis of focal and diffuse parenchymal diseases of the liver. Although US can detect liver cirrhosis in patients with decompensated liver function, it is not a suitable method for detecting acute changes [14—16]. These findings led to the study of several noninvasive laboratory and imaging methods for accurate determination of the amount of liver fibrosis in recent years. However, the diagnostic value of US and grayscale findings has not been fully investigated in a large series of patients. In this study, we assessed the value of the combination of grayscale and Doppler ultrasonographic findings in the diagnosis of liver fibrosis in patients with chronic viral hepatitis.

Materials and methods

Patients

In this cross-sectional study, conducted from June 2011 to February 2013, 60 patients with chronic viral hepatitis who were candidate for liver biopsy in the Gastroenterology Department of Imam Reza Hospital, hospital were enrolled according to the purposive sampling technique. Based on Hung et al's [14] study, using the formula:

$$N = z_{(1-\alpha/2)^2} \times P(1-p)/d^2,$$

we chose a sample size of 30 patients. Inclusion criteria were positive serum hepatitis B virus surface antigen (HBsAg) or antihepatitis C virus antibody along with abnormal serum alanine transaminase level in the past 6 months. Patients were excluded if they had any clinical and/or biochemical evidence of decompensated hepatic function or portal hypertension, known hepatic diseases of other etiology, and a history of oral contraceptive pills or other drugs known to be hepatotoxic, or any drugs with hemodynamic changes that may affect Doppler results.

This study was approved by the Ethical Committee of Mashhad University of Medical Sciences, Mashhad, Iran (no.: 87543). All patients had a signed informed consent form.

US examination

Grayscale and Doppler ultrasonography (DS) were performed by a Hitachi EUB 525 for all patients during the week prior to liver biopsy, with a 7.5 MHz linear and 3.5 MHz curved probes for grayscale US and a 3.5 MHz curved probe for DS.

The patients fasted for 6 hours prior to examination, and then were studied in supine and left posterior oblique positions. The radiologist who was blinded about the pathological results of the patients performed the examination.

Spleen and liver sizes; diameters of portal vein, intrahepatic veins, and splenic vein; and gallbladder wall thickness were measured in millimeters. Liver surface and hepatic parenchyma echogenicity were also recorded during grayscale US. Doppler parameters such as portal and hepatic vein blood velocities and directions, and wave patterns of blood flow were studied.

These variables were scored according to the ultrasonographic scoring system that has been summarized in Table 1 [14,17—19]. The total grayscale US score and DS score were calculated by the summation of individual scores for different variables that had been measured. Similarly, the total US—DS score was calculated from the sum of grayscale US and DS scores.

Percutaneous liver biopsy

Liver biopsy of the anterior segment of right lobe was performed by a hepatologist using a 16-gauge Tru-cut biopsy needle. Specimens were processed, and serial paraffin-embedded sections were prepared.

After staining with hematoxylin and eosin, an experienced hepatopathologist who was blinded to the ultrasonographic findings of the patients reviewed the specimens.

Table 1 Grayscale scoring system.

Score	Liver length	Echo pattern	Echogenicity	Liver surface	Spleen length (mm)	GB wall thickness (mm)	Main portal vein diameter (mm)	Hepatic vein diameter (mm)	Splenic vein diameter (mm)
0	≥150 mm	Homogeneous	Normal	Smooth	≤130	≤3	≤13	4–10	≤10
1	<150 mm	Heterogeneous	Mildly increased	Irregular	>130	>3	>13	<4 or >10 or nonvisible	>10
2			Moderately increased						
3			Severely increased						

GB = gallbladder.

Histopathology

Histological stage of the fibrosis and grade of the necroinflammation were scored according to the Ishak's Modified Histologic Activity Index on a scale of 0–6 for fibrosis and 0–18 for necroinflammation [20]. Necroinflammatory scores consist of periportal or periseptal interface hepatitis (piecemeal necrosis) scores (0–4); confluent necrosis scores (0–6); focal (spotty) lytic necrosis, apoptosis, and focal inflammation scores (0–4); and finally portal inflammation scores (0–4).

Statistical analysis

The results were analyzed by the SPSS version11.5 software (SPSS Inc., Chicago, IL, USA). Numerical variables were described as mean ± standard deviation. For the comparison of means in different groups, univariate analysis and Student–Newman–Keuls test were used. For the categorical variables, nonparameter analysis was used for the comparison. A p value < 0.05 was considered statistically significant. Logistic regression, Spearman's correlation, Kruskal–Wallis test, and Mann–Whitney test were used for analysis. Sensitivity, specificity, and positive predictive values of the US scoring system were calculated and compared with the results of the liver fibrosis stages.

Results

A total of 60 patients with a mean age of 35.6 ± 10.1 years were investigated. Baseline characteristics of patients are presented in Table 2.

Forty-five patients had abnormal liver specimens (75%) and different degrees of liver fibrosis. We found different ultrasonographic findings in different stages of liver fibrosis. A nonhomogeneous echo pattern in the liver was found in 35% of patients ($n = 21$). Staging of liver fibrosis was significantly related to the liver echo pattern ($p = 0.001$). Liver parenchyma echogenicity was slightly increased in 21.7% of patients, moderately increased in 21.7% of patients, and severely increased in 5% of patients (Fig. 1). Echogenicity was related significantly to staging of liver fibrosis ($p = 0.001$). Liver surface appearance was irregular in 5% of patients and was related significantly to liver fibrosis progression ($p < 0.001$). Gallbladder wall thickness was abnormal in patients with liver fibrosis and related to pathological staging ($p = 0.02$).

Right hepatic vein diameters ranged from 2.8 mm to 8 mm (mean: 5.1 ± 1.2 mm) and revealed a significant correlation with staging and grading of liver fibrosis ($p = 0.004$ and $p = 0.019$, respectively). No relation was found between splenic vein, portal vein, left and middle hepatic vein diameters, splenic size, and the severity of liver fibrosis. The overall grayscale US score was normal (0) in 36.7% of patients and abnormal (1–7) in 63.3% of patients. The total grayscale US score was significantly different between patients with liver fibrosis and those without fibrosis ($p = 0.03$).

In Doppler study, the mean portal vein velocity ranged from 8.1 cm/s to 31.7 cm/s (mean: 17.1 ± 5.1 cm/s).

A mean velocity of 15–18 cm/s was considered normal, and the cutoff value for portal vein velocity was considered 15 cm/s.

The mean portal vein velocity was abnormal in 40 patients (67.7%). The mean velocity of portal vein varied significantly in various stages of liver fibrosis ($p = 0.01$). Wave patterns of hepatic veins and portal vein were normal in all patients (Figs. 2 and 3). The total DS scores were significantly different between patients with liver fibrosis and those without fibrosis ($p = 0.03$). In addition, we found a significant correlation between the severity of liver fibrosis and the US–DS score ($p < 0.001$, $r = 0.6$).

An analysis of variance test showed a significant difference between grayscale US and Doppler US scores between different fibrosis stages ($p = 0.000$ and $p = 0.004$, respectively; Table 3).

Table 2 Baseline characteristics of patients.

Fibrosis stage	Parameters			
	Number of patients (male)	Age (y)	Hepatitis B, *n* (%)	Hepatitis C, *n* (%)
0	15 (11)	31.7 ± 8.2	13 (86.7)	2 (13.3)
1	15 (9)	39.6 ± 8.2	12 (80.0)	3 (20.0)
2	10 (5)	34.1 ± 10.0	8 (80.0)	2 (20.0)
3	12 (7)	31.5 ± 7.4	7 (58.3)	5 (41.7)
4	3 (2)	43.6 ± 18.6	1 (33.3)	2 (66.7)
5	3 (2)	37.0 ± 12.0	1 (33.3)	2 (66.7)
6	2 (1)	53.5 ± 9.19	1 (50.0)	1 (50.5)

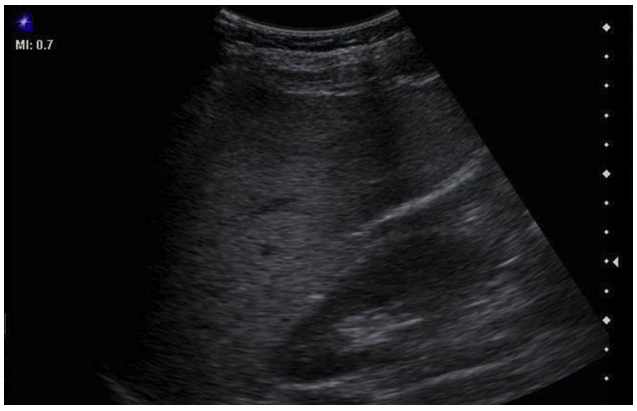

Fig. 1 Heterogeneous echogenicity in the liver parenchyma with a moderate increase in the overall echogenicity. Liver surface: smooth; spleen length: 110 mm; GB wall thickness, 2 mm; MPV: 11 mm; MHV: 6 mm; SV: 8 mm (grayscale score = 3). GB = gallbladder; MHV = hepatic vein diameter; MPV = mean portal vein velocity; SV = splenic vein.

According to receiver-operating characteristic curve results (Fig. 4), 1.5 is an appropriate cutoff point for grayscale US score, while it is 0.5 for Doppler US score for the prediction of the severity of liver fibrosis (Table 4).

To investigate the effect of simultaneous presence of US score and DS score parameters on fibrosis stages, logistic regression was used, which showed that the liver parenchymal echogenicity is the only parameter that is significantly related to fibrosis stages (95% confidence interval 0.011–0.738, $p = 0.025$).

Discussion

Viral hepatitis is a common cause of liver fibrosis worldwide. Some studies showed that 25–45% of patients with chronic viral hepatitis may develop liver cirrhosis and hepatocellular carcinoma [21]. Although liver biopsy is the gold standard method for its diagnosis, it is invasive and has

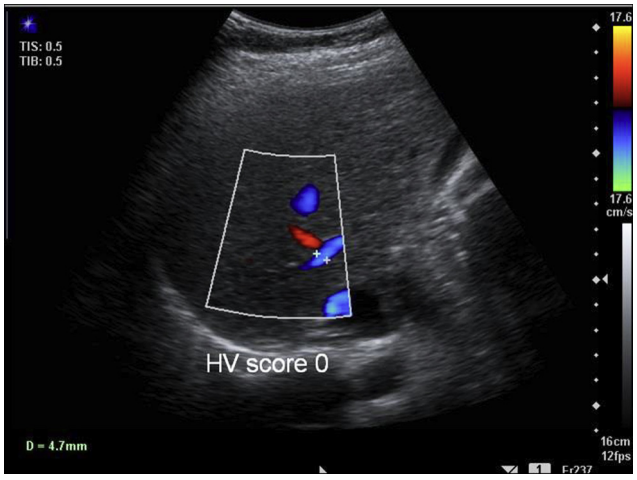

Fig. 2 Mean hepatic diameter (4.7 mm), which emphasizes a criterion for grayscale scoring (grayscale score = 0).

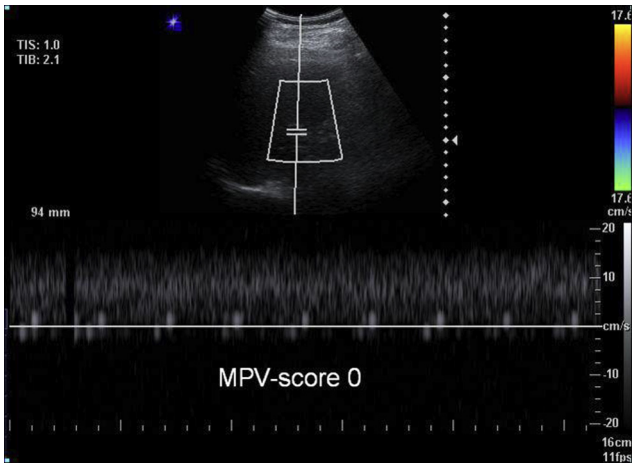

Fig. 3 Normal hepatopetal flow in the main portal vein of a patient (Doppler score = 0).

many complications. One of the most probable limitations of histological classification may be that liver tissue fibrotic changes do not always occur homogeneously, so a degree of failure can be present even at the level of the biopsy specimen. In recent studies, many authors suggest various noninvasive alternative methods such as serological tests or imaging methods. We studied the role of conventional US and DS as noninvasive methods for the diagnosis of liver fibrosis in 60 patients.

In our study, echo patterns of liver parenchyma and liver surface as well as liver parenchyma echogenicity were all related significantly to staging and severity of liver fibrosis. These results are compatible with Shen et al's [18] and Zheng et al's [17] studies. Zheng et al [17] used US in chronic hepatitis patients for the evaluation of hepatic inflammation and fibrosis degree, and compared them with the histopathological findings. They found that in moderate fibrosis, the diagnostic accuracy of ultrasound was significantly higher than that of serology. However, no significant difference was found between mild and severe fibrosis by the general diagnostic US. In addition, in Shen et al's [18] study, in patients with various stages of liver fibrosis, the echo pattern of liver parenchyma and the distribution of heterogeneous echogenicity was related to the severity of fibrosis.

Table 3 Mean and range of grayscale and Doppler US scores in each fibrosis stage.

Fibrosis stage	Grayscale US score		Doppler US score	
	Mean ± SD	Range	Mean ± SD	Range
0	0.73 ± 0.79	0–2	0.60 ± 0.82	0–2
1	1.40 ± 1.59	0–5	0.60 ± 0.73	0–2
2	1.70 ± 1.76	0–5	1.30 ± 0.82	0–2
3	1.58 ± 1.88	0–5	1.08 ± 0.51	0–2
4	6.00 ± 1.00	5–7	1.33 ± 0.57	1–2
5	4.66 ± 1.52	3–6	2.00 ± 0.00	2–2
6	4.00 ± 1.41	3–5	2.00 ± 0.00	2–2

SD = standard deviation; US = ultrasonography.

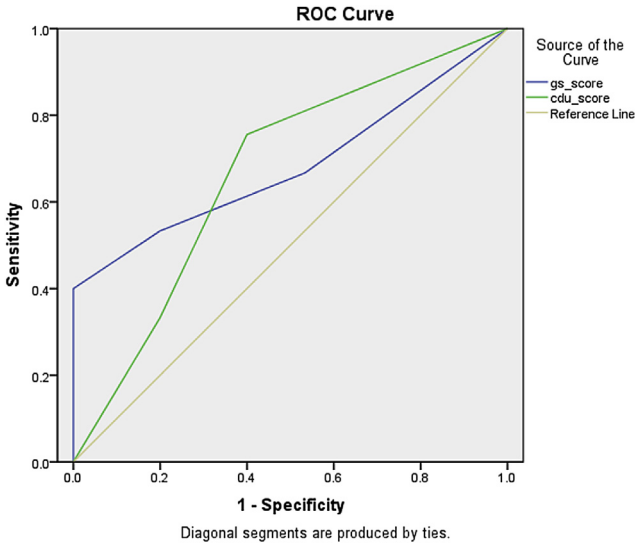

Fig. 4 ROC curve for grayscale ultrasonography score and Doppler ultrasonography for predicting the severity of liver fibrosis. ROC = receiver-operating characteristic.

The biliary system and the liver have somewhat similar histogenesis, anatomy, and function, which lead to accompaniment of viral hepatitis and biliary disorders. We also found a significant relation between gallbladder wall thickness and liver fibrosis staging, which was in agreement with other studies [17,22]. However, the mechanism is yet not clear. Although some factors such as direct invasiveness of hepatitis virus, immunity injury, secondary infections, and edema of the gallbladder might have a role in portal hypertension, circumfluence obstruction of the gallbladder vein, etc..

We did not find any correlation between the length of the spleen and fibrous staging of liver, which is contrary to the findings of Aube et al's [23] study. However, Shen et al [18] did not report any correlation between the spleen length and fibrosis staging score; however, they showed that the length of the spleen began to increase at S3 of liver fibrosis, but the length at S4 was not significantly different from that at S3.

Although diameters of all hepatic veins determined by grayscale US were correlated with liver fibrosis staging in Zheng et al's [17] study, in our research, this correlation was inverse and was found only in case of the right hepatic vein. In other words, the more the staging of liver fibrosis, the less the diameter of the right hepatic vein in grayscale US.

Similar to Gaiani et al's [21], Hung et al's [14], and Nishiura et al's [19] study, we found a significant correlation between total grayscale score and liver fibrosis. In Hung et al's [14] study, US scores correlated significantly with hepatic fibrosis scores ($p < 0.05$), in which the mean fibrosis scores were 0.95, 1.24, 2.35, 2.95, 3.8, and 3.7 in patients with US scores of 4, 5, 6, 7, 8, and 9 or more, respectively. An important point of Nishiura et al's [19] study is that individual parameters of US scores, such as liver edge, liver surface, and liver parenchymal texture, were significantly correlated with fibrosis stages determined based on the biopsy findings, but the total US scores of these three parameters were found to be the most reliable indicators (Spearman Rank-order Coefficient (rs): 0.9524).

The role of chronic viral involvement of liver in alternation of hemodynamic pattern of liver vascularity is a subject of controversy. A few studies showed a consistent relationship between DS findings and liver histology. Despite of Smith and Sterling's [24] study, Haktanir and coworkers [25] showed that Doppler US findings are sensitive to hemodynamic changes in liver fibrosis. These controversies may be related to the lack of a standard evaluating protocol for Doppler assessment along with the influence of different factors such as patient's age, extension of fibrosis, as well as cause of liver disease on hemodynamic indexes of hepatic vessels. In our study, Doppler US scoring was significantly related to liver fibrosis staging. Similar to Aube et al's [23] study, our data also showed a significant reverse correlation between the velocities of the main portal vein and fibrous staging of the liver.

So far, no study has evaluated a combined application of grayscale US and DS findings as a scoring system. The main strength of our research is that it was a prospective study, and our patients were uniform in a single etiology. In addition, we studied only nonalcoholic patients with no evidence of decompensated liver disease, in order to exclude the effect of alcohol steatosis and sever fibrosis in US findings. The limitation of our investigation was that the samples size was small; a future study should be conducted with a larger sample size.

In conclusion, in this study, we found that in the US scoring of the liver, liver parenchyma echogenicity was the only parameter related to fibrosis stages in logistic regression; therefore, liver parenchyma echogenicity may be enough and simple for use in clinical practice.

More importantly, we found that a combined US—DS scoring system could be a useful method for evaluating liver fibrosis. Further studies should be designed to evaluate the value of US findings in predicting liver fibrous staging in

Table 4 Diagnostic value of grayscale ultrasonography score and Doppler ultrasonography base on cut-off points for liver fibrosis.

Parameters and cutoff value	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Grayscale ultrasonography score (1.5)	40.0	100	0.682	0.100	0.35	—	0.6
Doppler ultrasonography score (0.5)	75.6	60	0.669	0.44	0.84	1.89	0.4

different types of chronic liver diseases. Establishing a standard US liver fibrosis scoring system will help clinicians to avoid invasive liver biopsies.

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